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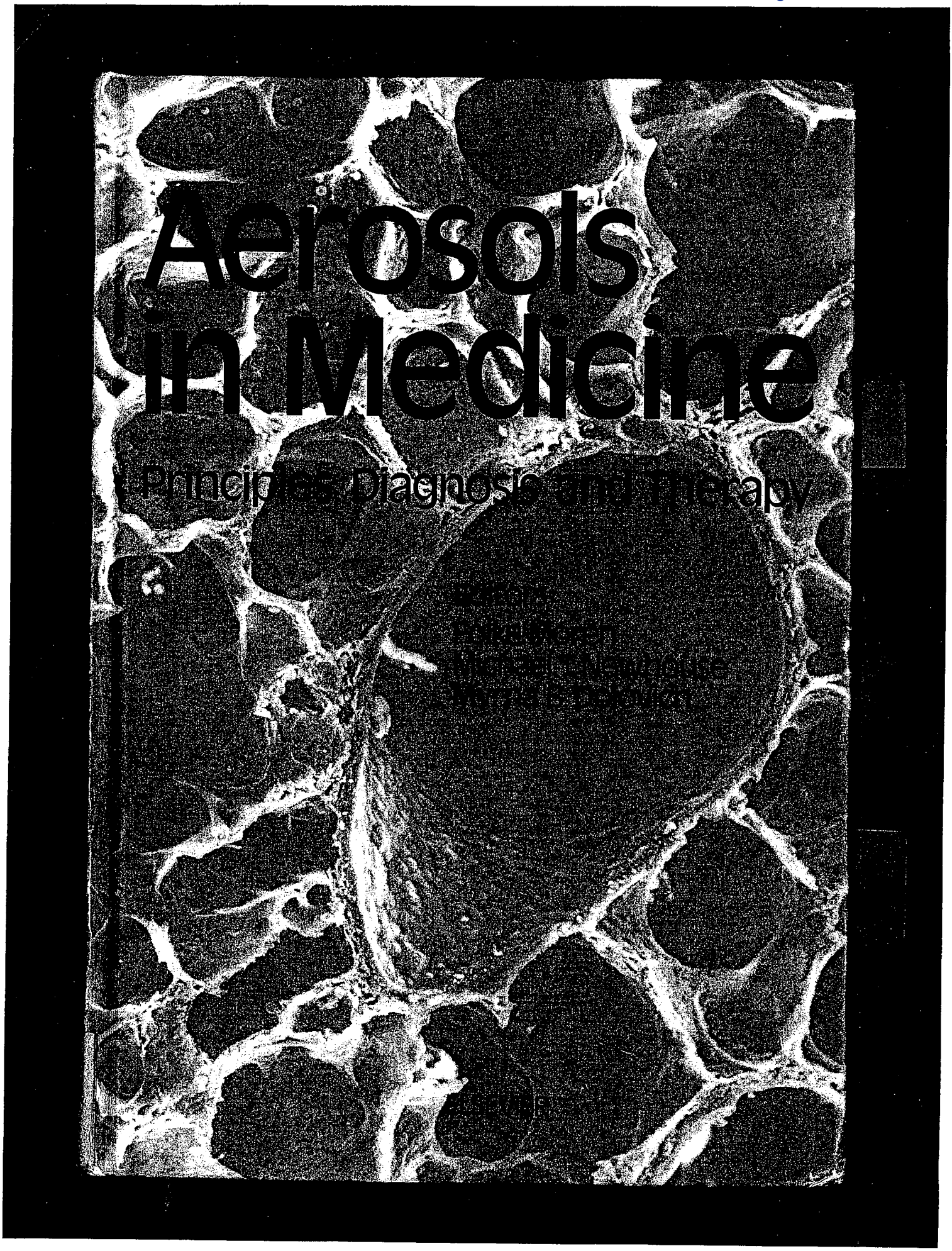
Aerosols
in Medicine
Principles, Diagnosis and Therapy

AEROSOLS IN MEDICINE
PRINCIPLES, DIAGNOSIS AND THERAPY

Edited by

FOLKE MORÉN, MICHAEL T. NEWHOUSE
and MYRNA B. DOLOVICH

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Aerosols in Medicine. Principles, Diagnosis and Therapy
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CHAPTER 1

Upper airway: structure, function and therapy

NIELS MYGIND

1. Introduction

For the purposes of this section, the division between upper and lower airways is taken as the junction of the larynx and trachea, as proposed by Proctor [1]. While the nose, pharynx and trachea are all part of the normal airway, the nose is bypassed when drugs are inhaled through the mouth. Therefore, one might ask why a book on 'Aerosols in Medicine' starts with a section on the nose. Firstly, there is increasing awareness that the airway should be regarded in a unified way, because stimulus-response relationships, associated with reflexes as well as the air-conditioning properties of proximal airways, may involve the entire respiratory tract. Secondly, the nose, which can be regarded as 'bronchi without smooth muscle', is easily accessible for investigations. Thirdly, patients requiring aerosol therapy because of lower respiratory tract disease frequently suffer from rhinitis as well, and aerosol therapy is also often applied to the nose. Finally, it would be tempting to treat allergic airways disease, affecting both nose and bronchi, via the natural route (i.e., nasal inhalation). This should give a deposition pattern similar to that of inhaled allergens, and may also decrease the deposition of drug in the pharynx. It might be worthwhile to explore this method of administration for sodium cromoglycate and glucocorticoids.

Since the nose will not be discussed later in this book, this chapter will give a broad presentation of the anatomy and physiology of the nose, the histopathology and physiopathology of rhinitis and intranasal aerosol therapy. More exhaustive reviews have been published elsewhere [1, 2]. Finally, the anatomy and physiology of pharynx and larynx are described.

2. *Anatomy of the nose*

The apparent external nose surrounds one-third of the nasal cavity, which in its entirety consists of a 4 cm high and 11 cm long dual chamber which reaches 'the centre of the head'. The total surface area of both nasal cavities is about 150 cm^2 and total volume is about 15 ml. About 1.5 cm from the nares is the narrowest portion of the entire airway, the internal ostium (or nasal valve), with a cross-sectional area of approximately 0.3 cm^2 in each nostril. The slit-like cavity is limited by the septal wall, seldom positioned exactly in the midline, and the lateral wall, dominated by inferior, middle and superior turbinates as well as the orifices of the nasolacrimal duct and the paranasal sinuses (Figs. 1 and 2).

The nasal vestibule is covered by skin, the anterior one-third of the nasal cavity by a squamous and transitional epithelium, the upper part of the cavity by an olfactory epithelium and the remaining portion by the typical ciliated pseudostratified columnar epithelium of the remainder of the airway.

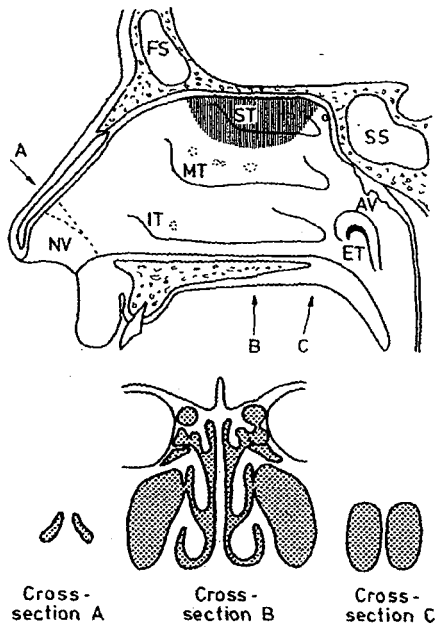

Figure 1. Lateral wall of the nasal cavity, and cross-sections through (A) the internal ostium, (B) the middle of the nasal cavity and (C) the choanae. Hatched area in the upper figure: olfactory region. NV, Nasal vestibule; IT, inferior turbinate and orifice of the nasolacrimal duct; MT, middle turbinate and orifices of frontal sinus, anterior ethmoid sinuses and maxillary sinuses, shown in antero-posterior direction; ST, superior turbinate and orifices of posterior ethmoidal sinuses; FS, frontal sinus; SS, sphenoidal sinus; AV, adenoid vegetations; ET, orifice of eustachian tube. From Mygind [2], by courtesy of Blackwell Scientific Publications.

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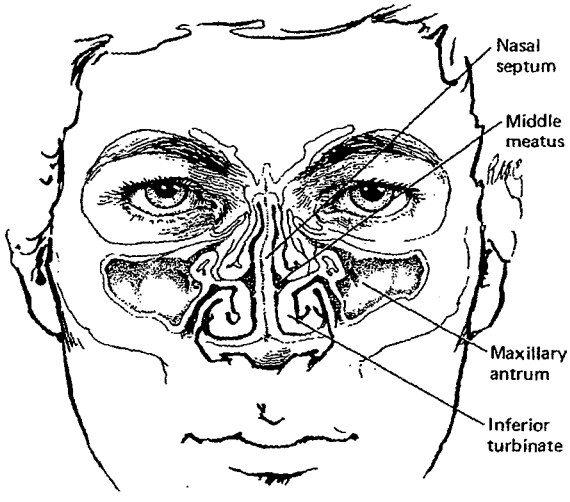


Figure 2. Section through the middle of the nasal cavity showing the slit-like nature of the nasal passage and relation to structures in the face. From Proctor [3], by courtesy of the author and McGraw-Hill Book Company.

The airway epithelium in the nose consists of four cell types (Fig. 3). In nasal biopsies taken with forceps from the inferior turbinate, 1–2 cm from its leading edge, the non-ciliated columnar cell is dominant and only about 10% of the surface is covered by cilia. When an epithelial biopsy is taken with curette or brush from the middle part of the inferior turbinate, there is a larger number of ciliated cells (approximately 25% of all epithelial cells). The cilia have a typical ultrastructure (Fig. 4), each ciliated cell containing about 100 cilia 0.3 μm wide and 5 μm in length (Fig. 5).

The number of goblet cells in the nose has been carefully mapped out by Tos and co-workers [5]. There are slight topographical differences, with a larger number in the posterior than in the anterior part of the nasal cavity. The mean concentration of goblet cells (4,000–7,000 cells per mm^2) is similar to that in the trachea and main bronchi [5].

The epithelium rests upon a layer of connective tissue, which under the light microscope is referred to as the 'basement membrane' (Fig. 3). In the bronchi this membrane is thickened in chronic asthma, while in the nose it is thickened both in rhinitis and in symptom-free individuals [6]. Since the nasal mucosa is affected by dry, unconditioned and polluted air, a 'normal' nose probably does not exist.

The lamina propria ('submucosa') is rich in blood vessels (Fig. 6). The arterioles are conspicuous by a total absence of the internal elastic membrane, so that the endothelial basement membrane is continuous with the basement membrane system of the smooth muscle cell. In addition, porosity of the endothelial basement membrane is one of the characteristics of the nasal blood vessels. As a result of these structural

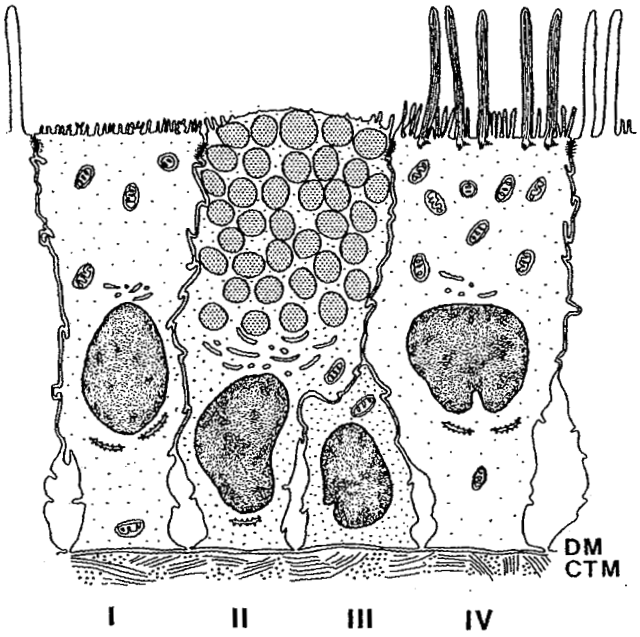
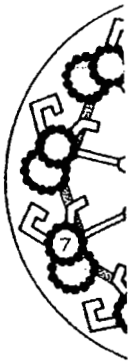


Figure 3. Transmission electron microscopic diagram of the four cell types in the nasal airway epithelium. I, Non-ciliated columnar cell, covered by microvilli of uniform length; II, goblet cell, packed with mucigen granules; III, basal cells; IV, ciliated columnar cell, covered by cilia and microvilli of uniform length. Many mitochondria in the luminal part of the cell. DM, Double membrane, which constitutes the electron microscopic basement membrane; CTM, connective tissue membrane, which together with the double membrane constitute the light microscopic basement membrane. From Mygind [2], by courtesy of Blackwell Scientific Publications.

characteristics, the subendothelial musculature of these vessels may be influenced more readily by agents, such as histamine and drugs, circulating in the blood stream than are blood vessels elsewhere. The capillaries just below the surface epithelium and surrounding the glands are of the fenestrated type. It is obvious that these capillaries are well suited for rapid movement of fluid through the vascular wall [7–9].

Large cavernous vascular sinusoids are located in the turbinates. These are normally found in a semi-contracted condition resulting from sympathetic nerve-mediated smooth muscle tone. The cavernous sinusoids are regarded as specialized vessels adapted to the functional demands of the nasal airway with respect to heating and humidification of inhaled air. Blood can bypass the capillary bed via arteriovenous anastomoses. Such anastomoses are found in the skin of the fingertips and toes, in the nail beds, lips and nose. At least half of the blood flow in the nasal mucosa is normally shunted through arteriovenous anastomoses [10]. Total blood flow per cm^3 of tissue is greater in the upper airway mucosa than in muscle, brain and liver [11].



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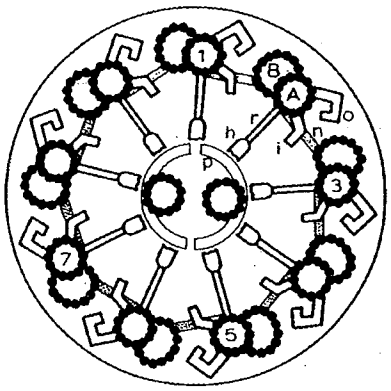

Figure 4. Detailed diagram of components seen in a transverse section of the middle part of the shaft of a cilium. The peripheral microtubule doublets are numbered clockwise (as seen from the basal end of the cilium, with dynein arms directed clockwise) and are composed of A and B microtubules; adjacent doublets are connected by nexin links (n), and the A microtubules bear outer (o) and inner (i) dynein arms extending toward the B microtubule of the adjacent doublet and spokes (h and r) which lie close to the central sheath (p) and the two single microtubules. From Sleigh [4], by courtesy of the author and Marcel Dekker.

The glands in the nose are of two types: anterior serous glands and small, scattered seromucous glands. There are only 100–150 anterior serous glands on each side. Their long excretory ducts have large openings in the upper part of the internal ostium (see Fig. 1), where small droplets of watery secretion can be seen through a magnifying glass, after stimulation of the nasal mucosa. It is not known exactly what role these glands play in the formation of watery rhinorrhoea, but there is little doubt that the small seromucous glands have a much larger secretory capacity. They have essentially the same structure as tracheo-bronchial glands. There are about 100,000 glands in the human nose, and this number appears to remain constant during life [5]. This suggests that an infant has a secretory capacity comparable to that of an adult, but a much smaller ciliated surface. Therefore, one can imagine that slight glandular hypersecretion may result in nasal discharge in the child, but not in the adult. The number of glands per unit surface area is considerably higher in the nose than in the trachea (eight versus one per mm^2), but this may not relate directly to secretory capacity, as nasal glands are smaller than tracheal glands [5].

Afferent nerve fibres run in the trigeminal nerve, and efferent parasympathetic fibres in the vidian nerve, while efferent sympathetic fibres follow the blood vessels. There is a rich parasympathetic innervation of the glands. Nervous stimulation of glandular cholinoceptors causes marked hypersecretion and is often part of a reflex arc. Blood vessels, having both sympathetic and parasympathetic innervation, are, on the other hand, controlled mainly by sympathetic fibres (Figs. 7 and 8). Continuous release of noradrenalin keeps the sinusoids partly contracted, as the vasoconstrictor

Figure 5. Scanning electron micrograph of the nasal mucosa showing partly ciliated epithelium. Some cells are covered by about 100 cilia (×2,475). From Mygind [2], by courtesy of Blackwell Scientific Publications.

effect from stimulation of the alpha-adrenoceptor is more marked than the vasodilatation from stimulation of the beta-2-receptor.

3. *Applied physiology of the nose*

The different functions of the human nose are depicted in Figure 9. The two major functions are olfaction, which will not be described further, and conditioning of the inspired air for the lungs. The 'piggy bank' function refers to the fact that the body saves about 100 ml of water per day, due to condensation of exhaled water in the an-

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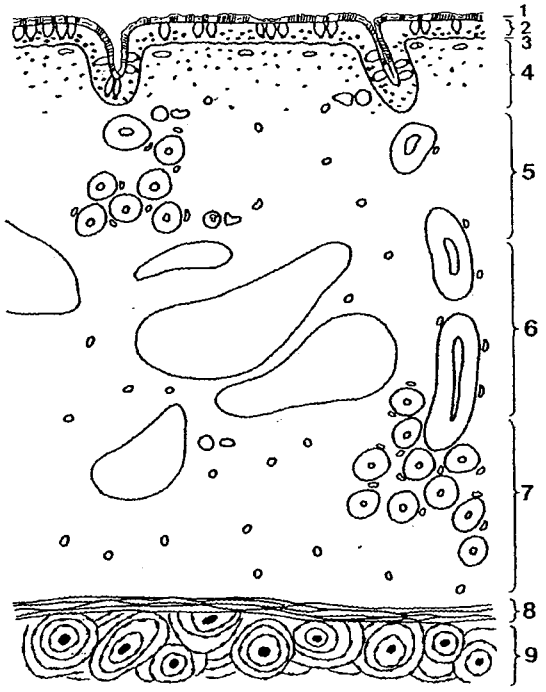

Figure 6. Diagram of the mucous membrane of the inferior turbinate. 1, Secretion layer; 2, ciliated pseudostratified epithelium; 3, basement membrane; 4, cell-rich subepithelial layer (fenestrated subepithelial capillaries, arterio-venous anastomoses and glandular ducts are indicated); 5, superficial glandular layer (fenestrated periglandular capillaries are indicated); 6, middle layer, containing cavernous sinusoids (continuous capillaries are indicated); 7, deep glandular layer; 8, periosteum; 9, bone. 4–7 constitute lamina propria. From Mygind [2], by courtesy of Blackwell Scientific Publications.

terior part of the nose, which has a temperature 3–4°C lower than that of the lungs. This water contributes to rhinorrhoea in cold weather.

3.1. Nasal airways

Nasal breathing is vital for most species, and also for neonates in the first weeks of life. Later, breathing through the mouth can sustain life, but suspended nasal airflow is both unpleasant and potentially harmful as the air-conditioning function of the nose is lost.

The normal nose is characterized by slit-like passages, which provide for efficient exchange of heat and moisture (see Figs. 1 and 2). Abnormal nasal airflow is characterized by reduced wall contact of the inspired air. The width of the nasal airway is actively regulated via the sympathetic innervation and tone in the venous sinusoids.

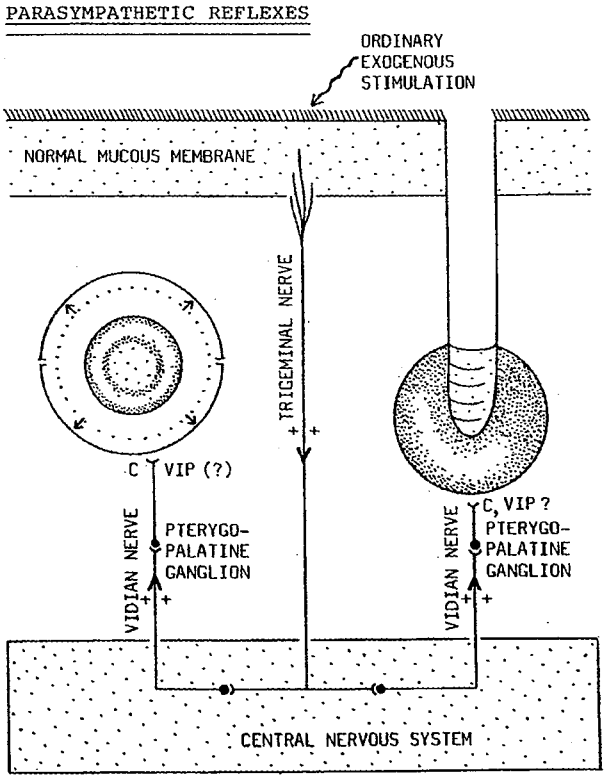

Figure 7. Stimulation of sensory nerves, e.g., by the unconditioned inhaled air, initiates parasympathetic reflexes, which cause significant hypersecretion, and slight, transient vasodilatation. C, Cholinoceptor; VIP, vasoactive intestinal polypeptide. From Mygind [12], by courtesy of The Journal of Allergy and Clinical Immunology, The C.V. Mosby Company.

This changes from one side to the other at 2–4-hour intervals. The nasal cycle is perceived only in subjects with a deflected septum and in patients with rhinitis.

3.2. Heating and humidification

The nose is well suited to its air-conditioning function: (1) The slit-like shape of the nasal cavity assures close contact between the inhaled air and the mucous membranes. (2) The width of the cavity can adapt rapidly to changing needs by alterations in sinusoid contraction. (3) Heat exchange is facilitated by the large amount of arterial blood flowing in arteriovenous anastomoses, analogous to hot water in a radiator. (4) The nasal mucosa has a high secretory capacity. As early as 1956 Ingelstedt [13] measured the air-conditioning capacity of the upper airway (mainly nose) and found

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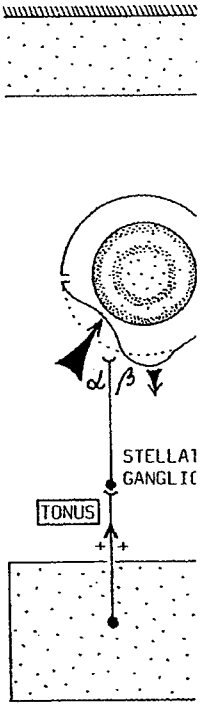

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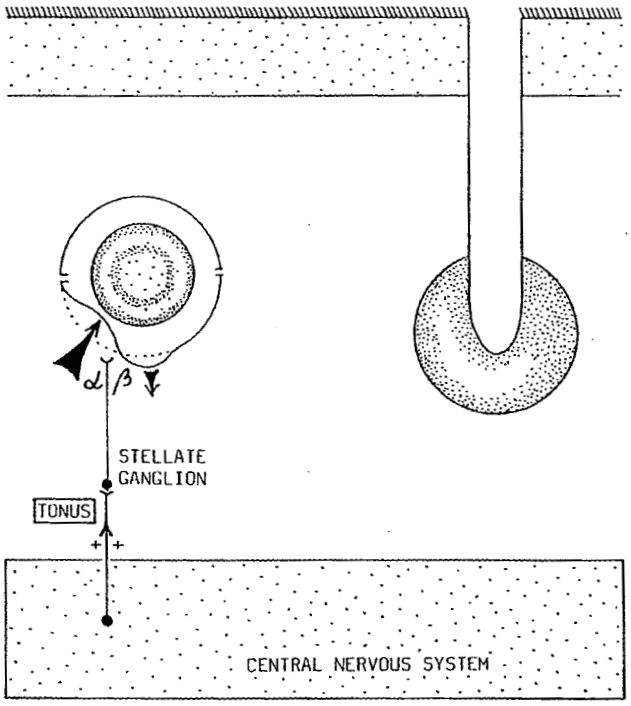


Figure 8. There is a continuous impulse traffic in efferent sympathetic fibres to the blood vessels, keeping them partially constricted. Action on alpha-1-adrenoceptors (α) causes marked vasoconstriction, and stimulation of beta-2-adrenoceptors (β) causes slight vasodilatation. From Mygind [12], by courtesy of The Journal of Allergy and Clinical Immunology, The C.V. Mosby Company.

that room air (23°C, 40% relative humidity) was conditioned to 32°C and 98% humidity by the time it reached the subglottic space. Corresponding figures for oral breathing were 30°C and 90%, and they varied with the extent to which the mouth was opened. After nasal breathing of cold air (−4–0°C) the figures were 31°C and 98%. This has been paraphrased by N.G. Toremalm: "A single sniff changes Scandinavian winter to Florida weather". In conclusion, the upper airway (pharynx, larynx and, especially, nose) heats and moistens the inspired air satisfactorily at room temperature, while mouth breathing conditions inspired air, at room temperature, less effectively than the nose does cold air.

The significance of this discussion has been emphasized by the recent demonstration that bronchial heat loss is an important factor in asthma induced by exercise, hyperventilation and cold air [14]. As many asthmatics also suffer from rhinitis, the significance of impaired nasal function in bronchial asthma deserves more detailed study.

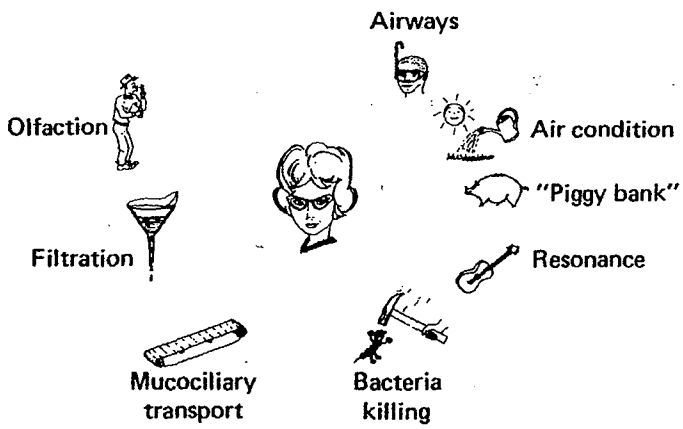


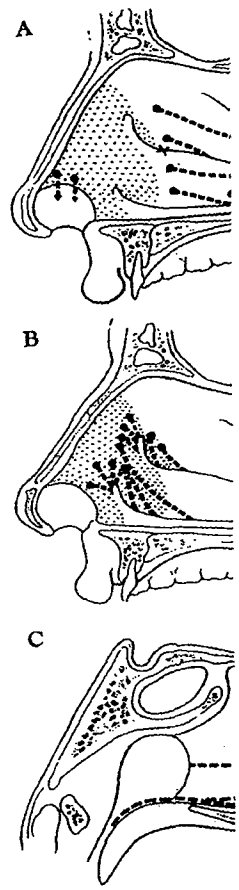
Figure 9. The function of the nose — as seen by the late Professor Sven Ingelstedt, University Department of Oto-Rhino-Laryngology, Malmö Hospital, Malmö, Sweden. Permission was obtained in 1977 [2].

3.3. *Filtration*

In contrast to the lower airway, damage to the nasal lining from inhaled noxious agents is not likely to be fatal, and the more proximally the inhaled particles are deposited, the more quickly they are removed (nose, minutes; bronchi, hours; alveoli, weeks). Therefore, deposition of inhaled particles in the nose is expedient. It is favoured by the shape of the nasal cavities, as turbulence and impaction cause deposition of particles distal to sites of constriction and where changes in the direction of airflow occur (see Fig. 1).

The nose is normally the principal site of particle deposition, but the efficiency of the nasal filter depends largely on the diameter of the particles inhaled. Only few particles larger than 10 μm (pollen grains) are able to penetrate the nose during breathing at rest, while most particles smaller than 2 μm (mould spores) bypass the nose. The nose also acts as a protective filter for water-soluble gases (sulphur dioxide, formaldehyde). The irritating and tissue-damaging sulphur dioxide is more than 99% retained in the nasal 'gas mask', even when the concentration (25 ppm) is much higher than in the most polluted city air [15].

Inhaled particles, trapped in the nasal filter, are cleared from the nose with a half-time of 30 minutes by mucociliary transport. As in all other parts of the airway, cilia beat in the direction of the pharynx, where mucus and trapped particles and micro-organisms are swallowed (Fig. 10). Cilia in the middle ear beat towards the eustachian tube, and in the paranasal sinuses beating and transport are directed towards their orifices.



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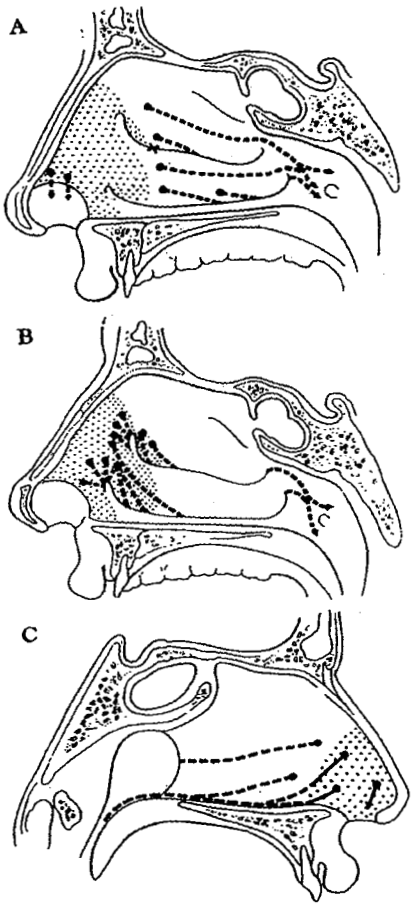


Figure 10. Pattern of mucociliary transport in the nose. A, The course of mucus flow on the lateral wall in the ciliated area and in the very front of the nasal cavity. B, The course of flow on the lateral wall in the non-ciliated area (dotted area). C, The course of flow of mucus on the septum. From the late Professor A.C. Hilding [16]. Permission was obtained in 1977 [2]. By courtesy of Archives of Environmental Health.

4. *Pathology of rhinitis*

It is not possible to give a complete review of the anatomy and physiology of the abnormal nose, as this has not been studied in sufficient detail. In particular, knowledge about the nose's air-conditioning function in rhinitis is lacking. The following section will deal with selected aspects of three types of rhinitis: (1) allergic, (2) infectious, and (3) congenital disease.

4.1. *Allergic rhinitis*

This is the most frequent allergic airway disease, affecting 5–10% of the population. Aerosol therapy is increasingly used, and recent studies of the mechanisms of nasal allergy favour topical therapy, at least in principle [2, 17].

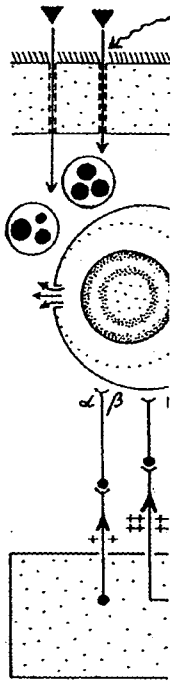
Histamine, the most important mediator of immediate allergic symptoms in the nose, causes itching, sneezing and hypersecretion, when it is placed as a droplet *on* the nasal mucosa, but only slight obstruction when it is injected *into* the mucous membrane, as shown by Okuda and Mygind [17]. This, and other observations, demonstrate that the closer to the mucosal surface histamine is released, the more marked the allergic symptoms. This is apparently because the effect of histamine is amplified by reflexes (Fig. 11). Since histamine is released from mast cells and basophils, the number of such cells in a nasal smear (secretion and epithelium) is probably important for the production of symptoms. The number of cells can vary from 0 to 1000, can be increased in seasonal allergic rhinitis, perennial rhinitis and nasal polyposis [18–20], and can be reduced by topical steroids [18, 20].

There is little doubt that histamine is mainly responsible for the immediate allergic symptoms in the nose, but it is not known what role leukotrienes, prostaglandins and other arachidonic acid metabolites play. It is possible that these mediators are responsible for the increased reactivity of the mucous membrane that is induced by allergen provocation and exposure [21]. Local eosinophilia, induced by eosinophilic chemotactic factor of anaphylaxis (ECF-A), is a characteristic feature of allergic rhinitis and of some types of non-allergic rhinitis (nasal polyposis).

4.2. *Primary ciliary dyskinesia*

Kartagener's syndrome consists of chronic rhino-sinusitis, chronic bronchitis with bronchiectasis and situs inversus. The airway symptoms are the consequence of a hereditary defect of cilia, which are immotile or have abnormal motility. This can also occur in individuals without situs inversus, and the entity is now referred to as 'primary ciliary dyskinesia' (also called the 'immotile-cilia syndrome', although most cilia are, in fact, motile [22]).

Not surprisingly, such patients have daily nasal discharge from birth, and nasal secretions generally contain both bacteria and many neutrophils [22]. It is interesting that these patients, without mucociliary transport, are no more prone to develop common colds than are normal subjects, suggesting that ciliary function does not protect against rhinovirus infection. All patients have chronic secretory otitis media, and chronic-recurrent sinusitis, but the frequency of acute purulent otitis media is not increased greatly. Furthermore, these patients usually do not develop serious invasive infections from the middle ear or sinuses which require surgery acutely. This suggests that although mucociliary transport is important for protection against superficial bacterial infections, it is not essential for protection against bacterial invasion of these tissues, provided that the other defence mechanisms are intact.



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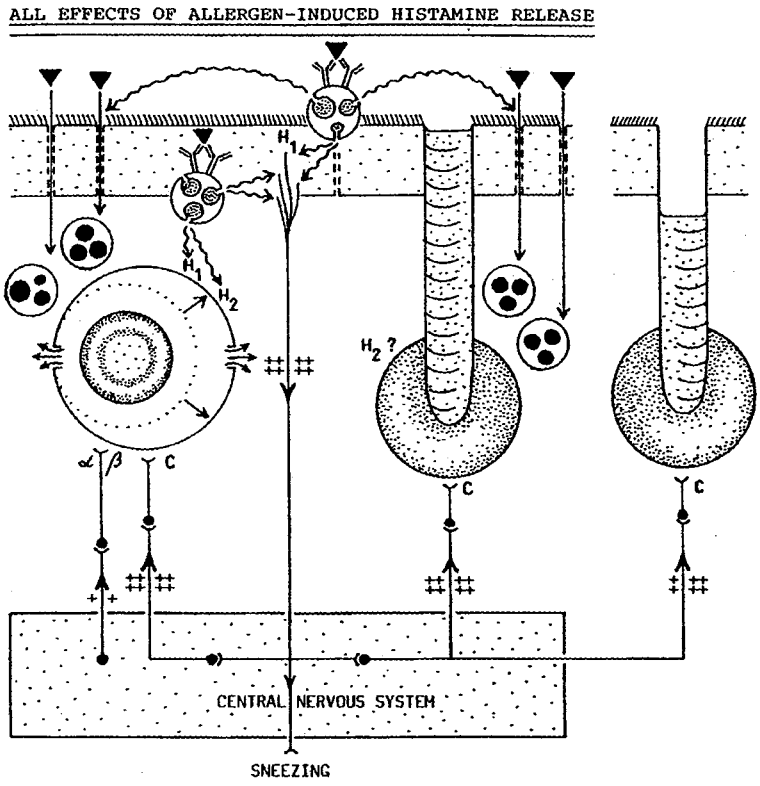

Figure 11. Simplified hypothesis of the pathogenesis of allergic rhinitis. Only the effects of histamine are included, since our knowledge of the significance of other biochemical mediators is still insufficient. Histamine acts in three ways. I, It increases the epithelial permeability and probably allergen penetration. II, It causes dilatation in some blood vessels and constriction in others, and oedema formation by a direct effect on vascular H_1 and H_2 receptors. Stimulation of glandular H_2 receptors possibly increases the release of glycoproteins without significantly affecting the total volume of nasal discharge, but this has not been shown in in vivo studies.

4.3. The common cold

Although this is such a common affliction, amazingly little is known about the pathohistology and pathophysiology. It is known from in vitro experiments that rhinoviruses cause a pronounced sloughing of the epithelial cells [23, 24]. A recent study has also shown that the number of ciliated cells, and with that mucociliary transport, is reduced considerably during a common cold and that these changes can last for weeks [25]. Although many epithelial cells are sloughed, the epithelial lining is not destroyed, but shows an intact surface on scanning electron microscopy [26]. Interestingly, neutrophils are recruited onto the nasal mucosa very early during a cold, when

no bacteria can be identified. Possibly, the viral infection itself stimulates local neutrophilia.

The beneficial effect of the cholinoceptor antagonist, ipratropium, as a nasal spray, on watery rhinorrhoea in the first 2–3 days of a cold [27] suggests that the early, but not the late symptoms of a cold, are reflexly mediated, at least in part.

5. *Aerosol therapy in the nose*

Drugs can be given in the nose as aerosols from pressurized aerosols and from metered-dose pump sprays, as solutions from drop bottles, and as powders inhaled from special devices. The drugs used for treatment of nasal disorders are alpha-adrenoceptor agonists (vasoconstrictors), cholinoceptor antagonists (ipratropium), sodium cromoglycate and glucocorticoids. As many drugs are absorbed readily and quickly from the airway mucosa, intranasal application can also be used for getting a drug into the circulation. As an example, pituitary hormones are administered effectively intranasally, avoiding decomposition in the gastro-intestinal tract. It has been shown recently that intranasal nebulization of the beta-2-adrenoceptor agonist, fenoterol, can give rapid bronchodilatation in asthmatic patients who are unable to inhale the aerosol [28].

Preservatives are necessary to prevent growth of bacteria and fungi in solutions designed for intranasal use. As the medication is often given to patients with hyperreactive mucous membranes, it is essential to choose non-irritating preservatives. Phenylethanol (0.4%) and benzalkonium chloride (0.01%) seem to be well-suited, because phenylethanol prevents the growth of *Pseudomonas* and benzalkonium chloride the growth of most other bacteria and fungi. As demonstrated in a controlled trial [29], they are non-irritating to normal nasal mucosa when delivered from a plastic bottle nebulizer. However, all aerosols and solutions, even saline, can provoke symptoms in some very hyperreactive rhinitis patients. With a solution of sodium cromoglycate [29] and with a pressurized steroid aerosol [30] local side-effects have been encountered more frequently during placebo than during active treatment. Thus, it would seem that the active treatment reduces the degree of hyperreactivity and so increases tolerance to intranasal medication.

Application of a large volume of a solution from a pipette or a drop-bottle gives a good distribution over the nasal mucosa, whereas a few drops do not. This is particularly important in the treatment of sinusitis, but correct administration is important in all conditions. Some patients, improperly instructed, will tilt the head backwards and pour the solution along the nasal floor to the rhinopharynx (Fig. 12).

A plastic bottle nebulizer will deliver a relatively large volume of solution in aerosol form. The distribution is acceptable in a normal nose, but in a blocked nose is inferior to that obtained with a drop-bottle. The dosage delivered from a plastic bottle varies considerably, depending on the force used to compress the bottle. Therefore, males usually will get a higher dose than females.

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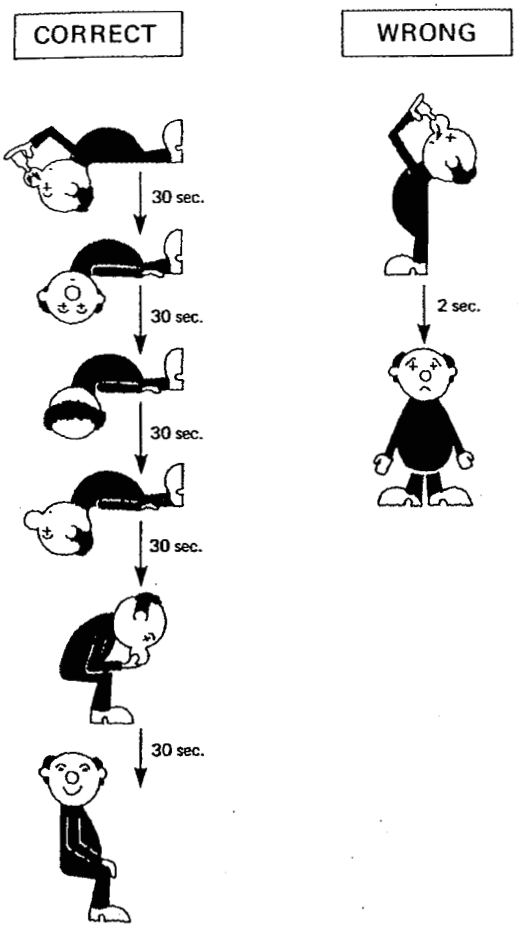

Figure 12. Illustration of correct and incorrect use of a vasoconstrictor delivered from a pipette or a drop-bottle. From Mygind [2], by courtesy of Blackwell Scientific Publications.

An atomized metered-dose pump spray, e.g., used for delivery of sodium cromoglycate, is not as simple and handy as the plastic bottle nebulizer, but it delivers a much more constant volume of the solution, which also is distributed more efficiently (Fig. 13). Since drug deposition depends on inhalation, droplets deposited in the nostril must be 'sniff-distributed'.

A very exact dose is also delivered from a metered-dose inhaler. It is safe to give potent drugs, such as steroids, in this manner. The manufacturer, by valve selection, can adjust the volume of propellants per puff, but no aerosol will deliver more than 2 mg of active drug per puff. The mucosal distribution of a drug delivered from a pressur-

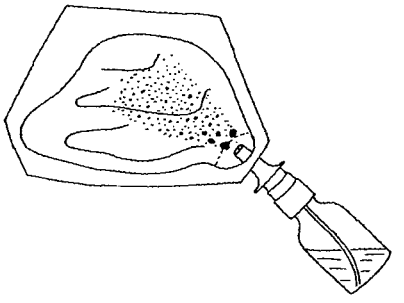

Figure 13. Diagram of intranasal drug deposition from a metered-dose pump spray. The distribution is good, but large droplets are always deposited in the nostril.

ized aerosol was studied in an artificial nose [31], demonstrating that the drug was not distributed evenly over the nasal mucosa (Fig. 14). While white propellant vapour was observed momentarily in all parts of the artificial nose immediately after delivery, only the anterior parts of the nasal cavity which received the full impact of the aerosol were coloured by a toluidine blue additive, the particle size of which was similar to that of the active drug. Drug deposition in the nose was independent of breathing pattern. Based on these results, we now recommend that our patients deliver one puff to the upper and one to the lower part of the nasal cavity. The patients are also told to hold the canister strictly in the saggital plane, because this will ensure optimal distribution between the lateral and septal wall. Without instruction the patient will point the nozzle against the nasal septum, where about 90% of the drug will be deposited. This is undesirable, because of the local irritation resulting from rapid cooling and drying of the mucosa by the propellants and the excessive focal deposition of the potent corticosteroid.

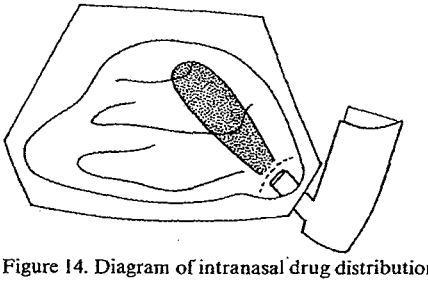

Figure 14. Diagram of intranasal drug distribution from a pressurized aerosol.

6. *Pharynx and larynx*

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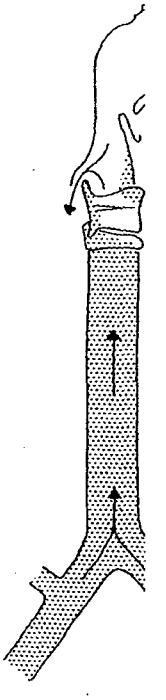

Figure 15. Diag
of mucus flow.

ciliated epithelium as is found in the nasal cavity (Fig. 15). There is no specific location where the airway mucosa changes to a stratified squamous epithelium, but this generally occurs in the area where the uvula and the soft palate touch the posterior and lateral walls of the pharynx during the act of swallowing. Both the oropharynx and the hypopharynx are lined by stratified squamous non-keratinized epithelium of the same type as that which covers the major part of the oral cavity.

In the larynx the epithelium varies according to its location. The entire pharyngeal surface of the epiglottis, the upper half of the laryngeal surface, a portion of the ventricular folds, and the true vocal cords are lined by stratified squamous epithelium. The lower half of the laryngeal surface of the epiglottis and the rest of the laryngeal cavity are lined by a pseudostratified ciliated epithelium (Fig. 15).

The lumen of the pharynx and larynx is shaped by bones, cartilages (Fig. 16) and a series of muscles, which participate in the acts of swallowing and speaking. The recent interest in the sleep apnea syndrome and its relation to upper airway function has resulted in some evidence that laryngeal muscles play a role in normal respiration.

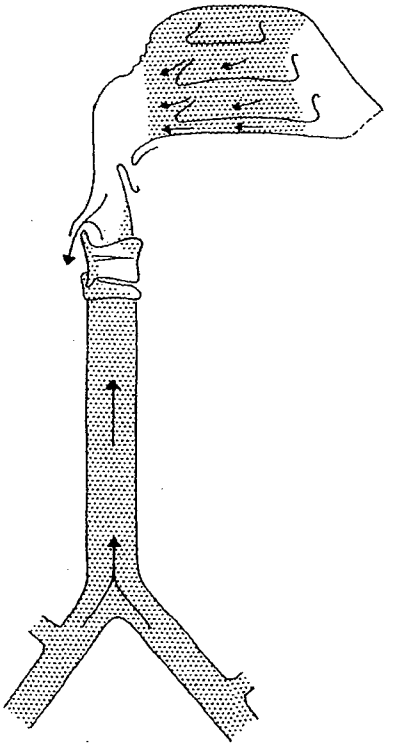

Figure 15. Diagram of ciliated epithelium in the airway (dotted area). The arrows indicate the direction of mucus flow.

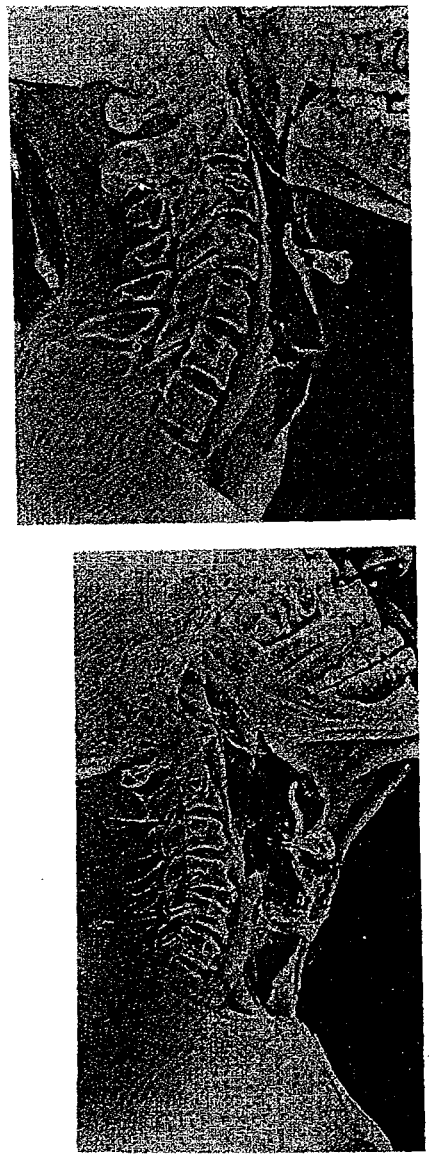

Figure 16. Xeroradiographs and diagram to identify key structures in pharynx and larynx. Note that backward bending of the head (lower xeroradiograph) increases considerably the distance between epiglottis and columna and straightens the route followed by an inhaled aerosol. From Proctor [32], by courtesy of the author and American Review of Respiratory Diseases.

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They dilate the pharyngo-laryngeal airway during inspiration and constrict it during expiration. Proctor, who has reviewed this topic extensively [32, 33], speculated that a function of these muscles is to stabilize the calibre of that part of the airway. He also pointed out that a mechanical obstruction or a functional collapse in any segment of the upper airways necessitates a greater pressure drop in the airway beyond that point in order to maintain airflow. Although the complete cricoid ring helps to protect against that effect, increased upper airway resistance can extend downwards into the extrathoracic trachea, where invagination of the membraneous wall will occur.

The pharynx and larynx can also influence lower airway diseases and their treatment in another way, as these regions act as barriers to aerosol therapy. While slow inhalation from a tube or a spacer can overcome partially the 'pharyngeal barrier', and allow more efficient lower respiratory tract aerosol deposition, nevertheless, large amounts of inhaled drug are deposited on the horizontally positioned vocal cords. This is supported by the failure to eliminate hoarseness, as a side effect of inhaled steroids, when the drug is inhaled slowly from a spacer. Recently, a valved holding chamber metered dose inhaler (MDI) add-on device (Aerochamber®) has been shown to reduce the upper airway aerosol dose about 10-fold, thus eliminating dysphonia almost completely [34].

It is well known that stimulation of laryngeal irritant or cough receptors can cause bronchoconstriction in asthmatics. It also has been claimed, but not confirmed, in man that stimulation of the pharyngeal mucosa can change tracheo-bronchial airway resistance [35]. Naso-bronchial reflexes, such as diving reflexes, are important in some animals (sea lions), and have also been described in man. However, reports are contradictory, and the significance of this reflex for the human airway is probably low.

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differential resulting from the patient's inspiratory effort during the administration of the aerosol. The use of positive pressure may increase the pressure differential. One method of increasing the pressure differential is by means of intermittent positive pressure breathing (IPPB), which increases the pressure differential during inspiration. It is debatable whether IPPB improves the efficacy of a nebulized drug [72]. It has been shown that IPPB produces less penetration, peripheral deposition and a lower total lung dose of radioactively labelled particles than does spontaneous breathing [73].

When the same drug is used for inhalation by means of a pressurized aerosol or nebulizer, the recommended dose for the nebulizer is always much higher. One may well ask oneself whether this means that the patients are being over-dosed or if the nebulizer is an inefficient aerosol generator. Alternatively, the difference might be due to the fact that nebulizers are used more often in treating patients who are seriously ill. In a dose-response study with salbutamol, it was found that the doses supplied by an IPPB jet nebulizer could be decreased while maintaining the same efficacy in mild asthmatics [74]. The percentage of nebulized solution that reaches the lungs varies in different studies [69, 74–77], and it is not easy to compare the results from the various studies as different types of nebulizers were used, the formulation of the liquids varied, and the modes of administration were different. It is evident that the fraction of the dose reaching the lungs will be different when the aerosol is administered through a face mask or a mouth piece or from a settling chamber. The particle size distribution of the generated aerosol will be affected by the passage of the aerosol through air [71] and large particles will be lost in the tubing.

From deposition studies, it is evident that the amount of water delivered from a nebulizer to the lungs is very low, and it is questionable whether this added liquid is of any clinical benefit. When terbutaline was administered as a pressurized aerosol via a holding chamber, the effects obtained in acute severe asthma were similar to those produced by the administration of the same amount of drug from a nebulizer [78]. Further studies comparing various aerosol systems in the same types of patients would be desirable.

4.2.2. Nasal pumps

A nasal pump can be designed to dispense a dose of 50 to 150 μl (see Fig. 9). The liquid passes from the multidose container through the capillary tube to the dosing chamber. During the initial actuation, the stem pushes a piston, which causes the air in the dosing chamber to be compressed. At a certain point on the stem, the compressed air escapes through a lateral opening. After the actuation has been completed, the stem returns to its original position. The piston starts to move upwards, and this creates a pressure differential within the dosing chamber which draws the liquid into the chamber through the capillary tube. Several actuations are needed before the tube and the dosing chamber have been filled with liquid. A dose of the liquid will then be dispensed through the actuator. The aerosol is formed in the actuator as the liquid